- Claim(s) 1-4, 7-26, and39-44 are pending in the application;
- Claim(s) 1-4, 7-26, and 39-44 are rejected; and
- Claim(s) 41 and 44 are objected to.

In the Claims

Applicants submit herewith a "marked-up" version of the claims. Applicants respectfully request entry of the contained amendments:

- Please cancel claims 41 and 42 without prejudice.
- Please amend claims 1, 39, 40, 43, and 44 as shown on the marked-up version of the claims.
- Please add claims 45, 46, 47, and 48.

The submitted marked-up version of the claims follows standard amendment rules, wherein added text has been underlined and deleted text has been bracketed. The status of all claims is also indicated.

Remarks to Amended Claims

Several amendments have been made to Independent Claims 1, 39 and 40:

- First, Claims 1, 39, and 40 have been amended to include that the genetic engineering cells are constructed "in vitro." Support in the specification for these amendments is found in several locations (several of these locations are footnoted below)[1,2,3]

- Second, Claims 1 and 39 have been amended to add that the electrical pulse maker is implanted. Several locations for support for these amendments are also footnoted.[4,5,6,7]

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1 **Page 7, Line 19:** "Figure 9: **In Vitro** Apparatus for Electrical Stimulation" (emphasis added)
2 **Page 7, Line 24:** "Figure 10: Electrical Stimulation Sequence for **In Vitro** Testing (emphasis added)
3 **Page 23, Line 26:** "Site directed mutagenesis of ANF-134GL and ANF-638GL was performed using the Promega Altered Sites **in vitro** mutagenesis kit according to the manufacturer's instructions." (emphasis added)
4 **Page 28, Line 13;** Generally this is accomplished by the **implantation of electrodes and leads for carrying the electrical stimulus from the electrical pulse generator** (Figure 1 represents the system used in the heart). (emphasis added)
5 **Page 34, Line 26;** It is envisioned that the **electrical pulse generator can be implanted** or can be external. (emphasis added)

- Third, Claims 1 and 39 have been amended to include that the implanted electrical pulsemaker is coupled to genetically engineered cells that have been implanted in a mammalian tissue. Please note a whole section in the specification is devoted to this topic as well as more individualized references.[8,9,10,11,12]

- Fourth, Claims 1, 39, and 40 have been amended to include that the system is capable of enhancing transcription.[13,14,15,16,17]

- Fifth, Claims 1, 39, and 40 have been amended to include that the promoter system is heterologous to the gene. Support for these amendments are contained in the specification as footnoted below.[18,19,20,21]

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[6] **Page 38, line 5:** The electrogram signal provided by EGM amplifier 76 is employed when the **implanted device** is being interrogated by an external programmer (not shown) to transmit by uplink telemetry a representation of an analog electrogram of the patient's electrical heart activity. (emphasis added)

[7] **Page 38, Line 20; This implantable pulse generator** has a power source that is a chemical battery to provide power to in-house electronics as well as to power the output circuitry to generate the electrical pulses to be delivered to the tissue. (emphasis added)

8 **Page 28, Line 1:** "Administering Cells to a Patient The genetically engineered cells containing an ERP may be introduced into a patient using known methods . . ."

[9] **Page 3, Line 7:** "The ERP gene constructs can be delivered by standard gene transfection methods to cells grown in culture and then implanted into the patient."

[10] **Page 36, Line 16:** "Alternatively, the pulse generator device can include stimulating elements similar to those used in **implantable nerve or muscle stimulators**, such as those disclosed in U.S. Pat. Nos. 5,199,428 (Obel et al.), 5,207,218 (Carpentier et al.), and 5,330,507 (Schwartz). (emphasis added)

[11] **Page 49, Line 21:** "Example 8: **Implantation of Labeled Cells** into the Myocardium after Ischemic Injury" (emphasis added)

[12] **Page 35, Line 1:** "Attaching lead and electrodes to the pulse generator are designed to **stimulate transcription** of at least one ERP." (emphasis added)

[13] **Page 10, Line 3:** 'Provided in the definition of Operably linked. "Thus, an ERP promoter sequence "operably linked" to a coding sequence refers to a configuration wherein the promoter sequence **promotes expression** (or inhibits the expression if a negative regulatory element) of the gene sequence upon electrical stimulation. (emphasis added)

[14] **Page 10, Line 3:** "Modulated **transcription may be positive** or negative, and may change the relative transcriptional amount over time by an amount that is equal to or approximately 2, 4, 6, 10, 20, 50, 100, or 1000 fold or greater than unstimulated cells over 1, 2, 4, 8, 16, 24, 48, or 72 hours." (emphasis added)

[15] **Page 10, Line 29:** "As referred to herein the promoter includes the 5' flanking sequences that **promote** transcription." (emphasis added)

[16] **Page 11, Line 24:** For example, an electrical response enhancer element is a region of DNA that, when associated with a gene operably linked to a promoter, **enhances the transcription** of that gene under conditions where the cells of the tissue provide an appropriate electrical stimulus." (emphasis added)

[17] **Page 14, Line 21:** For example, a "therapeutically effective amount" for a patient suffering or prone to suffering or being prevented from suffering a disease from a disease is such an amount which induces, ameliorates, or otherwise causes an improvement in the pathological symptoms, disease progression, physiological conditions associated with, or resistance to succumbing to a disorder principally characterized by an **increase in transcription** of a therapeutic product. (emphasis added)

[18] **Page 4, Line 27:** "In a related aspect, the invention includes a chimeric gene, containing an electrical response element which is **heterologous** to the therapeutic gene. Alternatively, the electrical response element is heterologous to the promoter."(emphasis added)

[19] "Two nucleic acid elements are said to be **"heterologous"** if the elements are derived from two different genes, or alternatively, two different species." (emphasis added)

Claims 41 and 42 have been canceled.

Claims 43-44 have been amended to be solely dependent on Claim 1 and to provide the proper antecedent basis to Claim 1 by reciting the preamble of Claim 1.

Claims 45-46 and 47-48 have been added to introduce a separate set of dependent claims originally found in claims 43-44. Claims 45-46 are dependent on Claim 39 and Claims 47-48 are dependent on Claim 40.

[20] **Page 12, Line 1:** The present invention also provides chimeric genes having at least three functional elements: (i) a therapeutic gene, (ii) a promoter, and (iii) an electrical responsive enhancer (ERE) element, wherein the ERE is heterologous to at least one of the other functional elements."
[21] **Page 46, Line 26:** "Example 5: ERP Promoters Linked to a Heterologous Gene"